International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 16, No. 2, 2026

Advances in Biomarkers for Sepsis-Associated Acute Kidney Injury

Zekai Pan [1, 3, *], Beigeng Liu [2, 3], Shan Ren [3]

[1] North China University of Science and Technology, Tangshan, Hebei, 063000, China
[2] Hebei Medical University, Shijiazhuang, Hebei, 050000, China
[3] Department of Critical Care Medicine, Hebei General Hospital, Shijiazhuang, Hebei, 050000, China

*** Corresponding author:** Zekai Pan (Email: panzekai10086@163.com)

Abstract: Sepsis is a leading cause of mortality among critically ill patients, and acute kidney injury (AKI) represents one of the most common complications associated with sepsis. Conventional diagnostic indicators, particularly serum creatinine, have limitations due to their delayed elevation after renal injury. Therefore, identifying novel biomarkers that enable early and accurate prediction of sepsis-associated acute kidney injury (SA-AKI) has become an important research focus.This review systematically summarizes recent advances in several biomarkers associated with SA-AKI, including proenkephalin A 119–159 (penKid), osteoprotegerin (OPG), galectin-3, presepsin, interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), C-C motif chemokine ligand 14 (CCL-14), urinary tissue inhibitor of metalloproteinase-2 × insulin-like growth factor-binding protein 7 ([TIMP-2] × [IGFBP7]), and calprotectin.By analyzing the diagnostic accuracy, prognostic value, and limitations of these biomarkers in the early detection and outcome prediction of SA-AKI, this review aims to provide new insights into early intervention strategies and improvement of clinical outcomes in patients with SA-AKI.

Keywords: Sepsis-associated Acute Kidney Injury; Biomarkers; Early Diagnosis; Prognosis; Renal Injury; Critical Illness.

1. Introduction

Sepsis is a severe disease. Currently, sepsis is commonly defined by Sepsis-3.0: life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. There are nearly 50 million new cases and 11 million deaths each year, making it one of the leading causes of death in critically ill patients. According to one study, the incidence of acute kidney injury (AKI) in multiple organ dysfunction caused by sepsis ranges from 45% to 70% [2].

At present, many studies [3-5] have shown that traditional serum creatinine- or urine output-based changes have certain limitations for the early diagnosis and prediction of SA-AKI. Therefore, new, more sensitive and specific biomarkers are currently needed for early detection and diagnosis of SA-AKI, so as to enable early prevention, early intervention, and early treatment, and thereby reduce the mortality of SA-AKI patients.

This review summarizes the biomarkers that can predict SA-AKI, evaluates the accuracy and limitations of these markers in predicting the occurrence of AKI, and seeks to identify more accurate and practical markers for predicting septic AKI, in order to further guide clinical practice.

2. Cystatin C

Cystatin C (Cys C), full name cysteine protease inhibitor, is a low-molecular-weight, basic non-glycosylated protein composed of 122 amino acids with a molecular weight of approximately 13.3 kDa [6]. In the human body, it is produced by nucleated cells and exists in extracellular fluid. Cys C is mainly metabolised in the kidneys; it is freely filtered through the glomeruli and reabsorbed in the proximal convoluted tubules, without being secreted by the renal tubules. It is negatively correlated with glomerular filtration rate and is a biomarker reflecting renal function. Serum Cys C concentration is independent of sex, age or muscle mass, all of which are typical confounding factors for assessing glomerular filtration rate. The serum concentration of Cys C depends almost entirely on renal function, so it is considered an ideal endogenous marker. Cys C as a potential biomarker for early prediction and diagnosis of AKI, or as a substitute for creatinine, has long been a subject of widespread attention. A study by Zhang Z showed that Cys C can serve as a biomarker for assessing the severity and prognosis of acute kidney injury [7]; an earlier meta-analysis indicated that serum Cys C is superior to serum creatinine in the timing of diagnosis of acute kidney injury [8]. In terms of SA-AKI, Wang Xin et al. observed 2331 septic patients in the ICU and found that higher Cys C, procalcitonin, and baseline creatinine values were independent risk factors for the development of acute kidney injury in septic patients, with an odds ratio (OR) of 7.046 for Cys C and 4.401 for creatinine [9]. Wei Maobi et al. showed that serum Cys C concentration was positively correlated with the severity of SA-AKI. For predicting the occurrence of SA-AKI, serum Cys C (sCysC) had an AUC of 0.883, sensitivity of 77.9%, and specificity of 88.1%, while admission creatinine had an AUC of 0.703, sensitivity of 63.2%, and specificity of 69.4%. This indicates that, before AKI occurs in sepsis, sCysC rises more rapidly than serum creatinine and can reflect changes in renal function earlier and more sensitively [10]. Recently, a prospective observational study found that Cys C (OR=4.139, 95% CI 1.727–9.919, P=0.001) was an independent risk factor for 28-day prognosis in SA-AKI patients, and the AUC of Cys C for predicting 28-day prognosis was 0.690 (95% CI 0.583–0.798, P=0.001) [11]. However, in clinical practice, Cys C is not as widely used as creatinine, and the reasons are considered to be its relatively higher testing cost and lower accuracy compared with creatinine [12]. Nevertheless, with the increasing awareness of Cys C among healthcare professionals and the continuous advancement of detection

techniques, Cys C may become a more sensitive and reliable new standard than traditional creatinine.

3. Proenkephalin A 119–159 (penKid)

Proenkephalin A 119–159 (Penkid) is an endogenous opioid peptide with a molecular weight of approximately 5 kDa. Penkid is mainly expressed in the kidneys; it has a long half-life and good stability in the human body, does not bind to plasma proteins, and is eliminated only through glomerular filtration. Therefore, it is also an ideal marker reflecting renal function [13]. In the field of SA-AKI, research on Penkid is relatively active. For early septic patients in the emergency department who develop AKI within 48 hours, the admission serum penKid concentration can effectively predict it, with an AUC of 0.756; however, compared with creatinine, its predictive ability is not as good, as the latter had an AUC of 0.875 in that study [14]. One study found that Penkid was an independent risk factor for AKI in septic patients in the ICU. ROC curve analysis showed that when the Penkid threshold was set at 2.41 μg/L, the area under the curve was 0.867, the sensitivity was 0.788, and the specificity was 0.832 [15]. In terms of prognosis, Pu Xuehua et al. found that the serum penKid concentration at ICU admission in the death group was significantly higher than that in the survival group. COX regression analysis showed that penKid (HR=5.892, 95%CI: 2.457–14.132, $P < 0.001$) was an independent risk factor for death in SA-AKI patients; the Kaplan-Meier curve showed that patients with penKid < 3.24 μg/L had a significantly higher 28-day overall survival rate than those with baseline penKid ≥ 3.24 μg/L ($P < 0.001$) [15]. In patients with subclinical acute kidney injury, although serum Penkid concentration was associated with 28-day mortality after ICU admission, its predictive value for mortality was not high, with an AUC of 0.66 [16]. At present, further research is still needed on the combination of Penkid with other biomarkers for predicting the occurrence and prognosis of subclinical acute kidney injury in critically ill patients.

4. Osteoprotegerin (OPG)

Osteoprotegerin (OPG) is a secreted protein belonging to the tumor necrosis factor receptor superfamily. OPG has been extensively studied in tumors, diabetes, and rheumatic diseases. In the field of sepsis, research on OPG is relatively limited. In 2017, Schaalan et al. found that serum OPG was significantly elevated in patients with sepsis and SA-AKI. The higher the OPG level, the worse the vascular endothelial function became in patients, and the changing trends of the two were the same. ROC analysis showed that OPG had similar specificity to the classic renal injury markers KIM-1 and cystatin C, with an AUC of 0.827 for OPG, 0.83 for KIM-1, and 0.82 for cystatin C. This result suggested that OPG could serve as a potential biomarker for SA-AKI [17]. Subsequently, Niu Xinrong et al. conducted animal experiments. To clarify the specific mechanism of OPG in SA-AKI, they found that OPG competitively binds to RANKL (receptor activator of nuclear factor-κB ligand) in sepsis-associated acute kidney injury, inhibiting the activation of the RANK (receptor activator of nuclear factor-κB)/TLR4 (Toll-like receptor 4) signaling pathway, thereby alleviating inflammatory responses and renal tissue damage. Recombinant RANKL treatment exerted a protective effect against SA-AKI by regulating the OPG/RANKL/RANK/TLR4 pathway. This pathway may become a potential therapeutic target for SA-AKI treatment [18]. However, current research on OPG in acute kidney injury is still scarce, and Schaalan et al. only collected serum from patients on the day of admission. Whether measuring serial serum OPG concentrations during hospitalization can predict the prognosis of SA-AKI patients, such as the transition from acute kidney injury to chronic kidney disease, or patient mortality, still requires more clinical studies to explore.

5. Galectin-3

Galectin-3 (Gal-3) is a β-galactoside-binding lectin that is widely expressed in multiple organs and tissues. It is mainly involved in processes such as inflammation and fibrosis, and regulates cell growth, proliferation, differentiation, phagocytosis, and exocytosis. Gal-3 has shown value as a potential biomarker in various diseases, including kidney and cardiovascular diseases, infection, autoimmunity, neurodegeneration, and malignant tumours [19]. In the field of sepsis, Mueller et al. found that serum Gal-3 concentrations in septic patients were significantly higher than those in healthy adults [20]. For SA-AKI patients, Sun et al. conducted a translational study and found that serum Gal-3 concentration at admission could predict the occurrence of AKI in septic patients, and could also predict 30-day all-cause mortality in these patients. Meanwhile, the researchers used a Gal-3 inhibitor in a rat model of septic kidney injury and found that inhibition of Gal-3 significantly reduced the levels of inflammatory cytokines, the incidence of acute kidney injury, and the 7-day mortality in the model rats, confirming that Gal-3 is an effective therapeutic target for S-AKI [21]. Hang Yi et al., after grouping SA-AKI patients according to the severity of kidney injury, found that the more severe the renal damage and the worse the disease progression, the higher the serum Gal-3 levels became. They also found that serum Gal-3 at admission had good diagnostic ability for SA-AKI, with an AUC of 0.867, which further confirmed the findings of Sun et al. [22]. In a recent translational study, Liu Lishan et al., using multiple AKI mouse models and clinical sample analysis, found that the transcription factor KLF4 in renal tubular cells could directly bind to and activate the expression of galectin-3. They generated a renal tubule-specific KLF4 knockout mouse model and intervened with a Gal-3 inhibitor. The results confirmed that blocking the KLF4/Gal-3 signalling pathway could effectively alleviate renal tubular injury and inhibit the inflammatory response, suggesting that this intervention strategy has the potential to become a promising therapeutic approach for acute kidney injury (AKI) [23].

6. Presepsin

Presepsin (PSP), also known as soluble CD14 subtype (sCD14-ST), is derived from soluble CD14 and can reflect the immune response status of monocytes and macrophages during bacterial infection. It is a marker of cellular immune response activation [24]. In the field of sepsis, Famhy et al. found that serum PSP concentrations increased significantly during bacterial infection in patients and decreased after infection control. They also found that the diagnostic accuracy and prognostic predictive ability of serum PSP for septic patients were comparable to those of PCT and superior to those of CRP [25]. Yuichiro et al., by measuring the dynamic changes of serum PSP in critically ill patients,

investigated whether PSP could be a predictor of septic acute kidney injury, initiation of renal replacement therapy in septic patients, and prognosis of septic AKI patients. The results showed that, in predicting renal replacement therapy, serum PSP on day 2 and its dynamic decrease from day 1 to day 5 both demonstrated extremely high predictive accuracy, with areas under the curve of 0.9 and 0.93, respectively. In addition, PSP also showed good predictive value for the occurrence of SA-AKI [26]. Yuichiro Shimoyama conducted an observational study to determine whether serum PSP and PLR levels during hospitalisation could predict the progression from subclinical septic acute kidney injury to overt septic AKI in ICU patients. His results found that PSP levels measured on days 1 and 2 after ICU admission could, to some extent, predict whether subclinical septic AKI would progress to overt septic AKI. However, in multivariate logistic regression analysis, the inflammatory marker PLR was identified as an independent predictor, while PSP was not included in the final model. This suggests that the predictive information provided by PSP may overlap with other inflammatory markers such as PLR, and its predictive role may not be entirely independent [27]. In a recent retrospective study, Suyeon et al. found that, among patients with severe renal injury who had already initiated CRRT, the role of PSP in diagnosing sepsis was surpassed by CRP and PCT, and it did not show independent prognostic predictive value. This study further found that PSP levels were negatively correlated with glomerular filtration rate, suggesting that its concentration is influenced by glomerular filtration rate rather than solely by the severity of infection [28]. In summary, PSP is a novel biomarker for sepsis, but its specific mechanisms in SA-AKI still require more basic and clinical studies for further investigation.

7. Interleukin-18

Interleukin-18 (IL-18) is a cytokine derived from proximal tubular epithelial cells, intercalated cells of the collecting duct, and macrophages from the bone marrow. IL-18 is cleaved by caspase-1 and released into the renal tubular lumen and serum, leading to neutrophil infiltration and further tubular injury [29]. In studies on IL-18 in the field of SA-AKI, as early as 2016, Zhou et al. found that IL-18 expression levels were significantly elevated in SA-AKI patients compared with non-AKI patients and healthy controls. The serum IL-18 at ICU admission for predicting AKI in septic patients had an AUC of 0.910 (95% confidence interval: 0.834-0.985), with a sensitivity of 78.60% and a specificity of 91.00% [30]. Wu Yanli et al. found that IL-18 levels were higher in septic patients with severe AKI than in those with mild AKI ($P < 0.05$), indicating that IL-18 levels are correlated with the severity of septic AKI [31]. Zhao Liang et al. conducted a prospective observational study and found that serum IL-18 at ICU admission had an AUC of 0.865 (95% confidence interval: 0.776-0.954) for predicting 28-day mortality in SA-AKI patients [32]. A meta-analysis examined the diagnostic characteristics of blood and urine biomarkers for sepsis-associated AKI. The study found that, based on the area under the ROC curve, the diagnostic order of biomarkers for sepsis-associated AKI was urine KIM-1 > urine NGAL > blood NGAL > urine IL-18. This indicates that IL-18 has a less favourable diagnostic value for SA-AKI compared with common AKI biomarkers [33]. In addition, it should be noted that IL-18 is a pro-inflammatory cytokine that plays an important role in sepsis, and IL-18 measurement may also be interfered with by many variables such as inflammatory and autoimmune diseases. Therefore, its sensitivity and specificity may also be affected.

8. Kidney Injury Molecule-1 (KIM-1)

Kidney injury molecule-1 (KIM-1), also known as T-cell immunoglobulin mucin receptor-1 (TIM-1), is a transmembrane protein mainly present on the epithelial cells of the proximal renal tubules. KIM-1 is almost undetectable in the kidneys of healthy individuals, whereas after patients experience shock or receive nephrotoxic drugs, KIM-1 has been found to be abundantly expressed on the apical membrane of proximal tubular cells [34]. Studies have shown that, compared with serum creatinine, KIM-1 demonstrates advantages in predicting proximal tubular injury and is a more ideal indicator of renal injury [35]. Further research by Bonventre found that, in AKI patients, KIM-1 serves as a highly specific and sensitive early biomarker, and its urinary levels can predict proximal tubular cell injury earlier than serum creatinine and blood urea nitrogen [36]. In a prospective study by Brozat JF, it was found that serum KIM-1 concentrations in AKI patients and septic patients in the ICU were significantly elevated compared with other critical illnesses, and the highest KIM-1 concentrations were observed in SA-AKI patients [37]. Tu Yuexing et al. conducted a prospective study of 150 SA-AKI patients [38] and found that, after the occurrence of sepsis-associated renal injury, KIM-1 levels began to rise at 6 hours and remained highly expressed up to 48 hours; the higher the concentration, the worse the patient's prognosis might be. Certainly, urinary KIM-1 combined with other biomarkers has greater predictive value for the early diagnosis of septic AKI and for assessing prognosis [39,40]. Based on the above studies, KIM-1 is a sensitive early marker for the diagnosis of SA-AKI, and its persistent elevation indicates a poor prognosis, thereby holding significant clinical value.

9. Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL) is a secretory protein of activated neutrophils and is expressed in multiple human tissues, including the kidney, heart, liver, and lung. In the kidney, it is mainly produced by renal tubular epithelial cells. Under normal conditions, the concentration of NGAL in urine is extremely low and difficult to detect, but it is significantly elevated in patients with acute injury or chronic kidney disease, and regenerating renal tubular epithelial cells also produce large amounts of NGAL during the repair process [41]. In an earlier prospective study, it was found that in the early stage of renal injury, elevations in plasma and urine NGAL levels could occur approximately 48 hours earlier than serum creatinine [42]. In recent studies, it was observed that when serum NGAL alone was used to predict SA-AKI, its AUC reached 0.875 [43]. Hong et al. conducted a prospective study on septic patients admitted to the emergency department. They measured urine NGAL levels and its ratio to creatinine at three time points: the first 24 hours after admission, 24-48 hours, and at the time of AKI diagnosis. The results showed that urine NGAL and its ratio to creatinine were effective early predictors of acute kidney injury in emergency septic patients. Meanwhile, urine NGAL measured within 48 hours of admission also demonstrated good predictive ability for mortality risk [44]. Regarding the prognostic value of NGAL in SA-AKI patients, Zhang et al.

studied 425 patients with sepsis-associated acute kidney injury, focusing on the dynamic changes in blood and urine NGAL levels before and after 48 hours of treatment, and evaluating their predictive value for subsequent CKD progression. They found that in patients with renal function recovery, both blood and urine NGAL decreased significantly after 48 hours, whereas in patients who eventually developed CKD, NGAL levels did not show a significant decrease. Further analysis revealed that, after adjusting for other factors, only the degree of decrease in blood NGAL was a reliable predictor of CKD development, while the predictive role of urine NGAL was relatively limited [45]. It is worth noting that the systemic inflammatory response caused by sepsis can lead to non-specific elevation of NGAL, which limits its differential diagnostic value in patients with concurrent AKI, because high NGAL levels may originate from the inflammation itself rather than from renal injury [46]. Therefore, in septic patients, even in the absence of AKI, its concentration can increase significantly, which may lead to false positives in AKI diagnosis.

10. C-C Motif Chemokine Ligand 14 (CCL-14)

C-C motif chemokine ligand 14 (CCL-14) is a class of small molecular proteins that direct chemotactic cell migration. CCL-14 is associated with tumours, immune-related diseases, acute kidney injury, and sepsis, among which research on the relationship between CCL-14 and AKI is currently relatively limited [47]. In the RUBY study, urinary CCL-14 was confirmed to be the optimal biomarker for predicting persistent severe acute kidney injury, with its predictive ability significantly superior to known AKI biomarkers such as urinary KIM-1, plasma cystatin C, and urinary NGAL. However, it is worth noting that some patients with multiple comorbidities had elevated CCL-14 levels even without developing persistent AKI, suggesting that the coexistence of AKI with other diseases may interfere with the interpretation of this marker [48]. A study by Fu You also showed that, among patients without stratification by AKI severity, urinary CCL-14 performed well in predicting persistent AKI; however, in patients with mild AKI, urinary CCL-14 did not show good predictive ability for persistent AKI [49]. In SA-AKI, a prospective observational study demonstrated that, in patients with stage 2-3 SA-AKI, urinary CCL-14 had higher predictive ability for non-recovery AKI compared with [TIMP-2] × [IGFBP7], with an AUC of 0.901 for CCL-14 and 0.730 for [TIMP-2] × [IGFBP7] (P = 0.001) [50]. A recent study from the Northern Jiangsu People's Hospital also showed that CCL-14 had good predictive ability for the development of persistent SA-AKI in septic patients (AUC = 0.821) [51]. However, the relationship between urinary CCL-14 and progression to persistent severe AKI in SA-AKI patients is currently unclear, and further research in this direction is needed in the future.

11. [TIMP-2] × [IGFBP7]

Tissue inhibitors of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) are biomarkers related to cell cycle arrest, and are also G1-phase cell cycle inhibitory proteins expressed and secreted by renal tubular cells. The product of the two can effectively predict the risk of severe AKI within 12 hours after testing [52]. In SA-AKI, Honore PM analysed data from 232 septic patients from 39 ICUs to observe the ability of urinary TIMP-2 and IGFBP7 to predict moderate-to-severe acute kidney injury within 12 hours, and to verify whether their predictive value was affected by other organ failures. The results showed that their urinary concentrations were significantly higher than in patients without acute kidney injury ($p < 0.001$). The areas under the receiver operating characteristic curves (95% CI) for TIMP-2 and IGFBP7 were 0.84 (0.73-0.92) and 0.85 (0.76-0.94), respectively, and the predictive performance of TIMP-2 and IGFBP7 was not significantly affected in patient subgroups with different SOFA scores [53]. This indicates that these two biomarkers have good value for early diagnosis of SA-AKI. In a recent study on the construction of a prediction model for AKI in septic patients based on three indicators, the researchers found that, compared with Ang-2 and PCT, the OR value of [TIMP-2] × [IGFBP7] was 2.71, much higher than that of Ang-2 (1.19) and PCT (1.05) [54]. In terms of prognosis, a prospective observational study showed that the product value of TIMP-2 and IGFBP7 could be used to assess the long-term prognosis of patients with established renal injury, and could identify high-risk patients who would die or require renal replacement therapy [55]. Another study found that early urinary [TIMP-2] × [IGFBP7] in septic shock was an independent risk factor for progression from mild and moderate AKI to severe AKI within the next 24 hours, and [TIMP-2] × [IGFBP7] > 2.0 $(ng/ml)^2/1000$ increased the risk of KDIGO stage 3 AKI by four-fold within 24 hours. This indicates that [TIMP-2] × [IGFBP7] can effectively predict the short-term prognosis of SA-AKI patients [56]. A recent study showed that urinary TIMP-2 and IGFBP-7 measured 2 hours after the furosemide stress test (FST) could dynamically assess renal tubular reserve function; combining this indicator could independently predict the need for RRT within 7 days, helping to identify patients who may require dialysis early [57]. In summary, TIMP-2 and IGFBP7 have high value for early diagnosis and prognosis in SA-AKI patients. In the future, it may be possible to combine [TIMP-2] × [IGFBP7] with other biomarkers to further investigate its clinical application value in SA-AKI.

12. Calprotectin

Calprotectin is a protein derived from neutrophils and monocytes, belonging to the S100 family, and consists of a heterodimer composed of S100A8 and S100A9 subunits. Calprotectin is abundant in neutrophils and is released into the blood upon cellular stress [58]. Calprotectin has high research value in inflammatory bowel diseases such as Crohn's disease and neonatal necrotising enterocolitis. In the field of sepsis, relevant research has also been relatively active in recent years. In 2016, Huang et al. found that serum calprotectin concentrations were significantly elevated in postoperative septic patients compared with healthy controls, and could serve as a diagnostic marker for sepsis in postoperative ICU patients [59]. Jing et al. found that, in septic patients admitted to the ICU, the AUC of calprotectin for predicting 28-day mortality was 0.617 (P = 0.032; 95% CI 0.513-0.721). Moreover, septic patients with high calprotectin concentrations (≥ 377.53 ng/mL) had higher survival rates than those with lower concentrations (< 377.53 ng/mL). This indicates that serum S100A8/A9 concentration at ICU admission is an important predictor of 28-day mortality risk in septic patients [60]. In terms of SA-AKI, Qian Jun and Xu Jianru et al. found that in animal experiments, blood calprotectin could not predict AKI in septic mice, whereas

urinary calprotectin could predict the early occurrence of SA-AKI in mice [61]. In septic patients, both blood and urinary calprotectin concentrations in the AKI group were higher than those in the non-AKI group, with statistically significant differences ($P < 0.05$), and the areas under the curve for serum calprotectin and urinary calprotectin were 0.655 and 0.883, respectively. This suggests that urinary calprotectin detection has greater advantage when AKI occurs in septic patients [62]. Another animal experiment observed that calprotectin expression was significantly elevated in the kidneys of septic mice. Treatment with an S100A9 inhibitor successfully alleviated renal dysfunction and renal tissue injury, suggesting that inhibiting calprotectin activity may become a novel therapeutic approach for septic acute kidney injury [63]. Recently, Zhao Mingyan et al. found that the calprotectin subunit S100A9 is a key molecule driving pyroptosis in septic acute kidney injury. It activates the NLRP3 inflammasome pathway, leading to caspase-1-dependent pyroptosis, thereby exacerbating renal inflammation and tissue damage. Therefore, S100A9 represents a potential therapeutic target. Inhibition or knockout of S100A9 significantly alleviated renal injury and pyroptosis, providing a new direction for researching the prognosis of patients with septic renal injury [64]. Calprotectin is an emerging biomarker in the sepsis field and has great research prospects in SA-AKI; further studies are still needed to explore its mechanisms and clinical applications in SA-AKI.

13. Summary and Future Perspectives

Reviewing the above various serum and urine biomarkers, such as Cystatin C, penKid, NGAL, KIM-1, and CCL-14, have demonstrated potential superior to the traditional indicator serum creatinine in terms of early diagnosis, risk stratification, and prognostic prediction of SA-AKI. In addition, some other feasible detection indicators have been mentioned in certain studies, including other interleukins besides IL-18, such as IL-6, IL-8, and IL-17. Moreover, L-FABP, PTGS2, and sTREM-1 have also been the subject of relevant research in SA-AKI; however, research on their clinical implementation is relatively scarce or difficult to carry out, and further exploration is still needed in the future. Furthermore, the specificity of most markers is susceptible to interference from systemic inflammation. Future research directions should still focus on combining multiple markers to predict the occurrence and prognosis of SA-AKI.

References

[1] Singer, M., Deutschman, C. S., Seymour, C. W., & et al. (2016). The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA, 315(8), 801-810. https://doi. org/ 10. 1001/jama.2016.2858.

[2] Hoste, E. A. J., Bagshaw, S. M., Bellomo, R., & et al. (2015). Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Medicine, 41(8), 1411-1423. https://doi.org/10.1007/s00134-015-3887-y.

[3] Ferreira, G. S., Frota, M. L., Gonzaga, M. J. D., & et al. (2024). The role of biomarkers in diagnosis of sepsis and acute kidney injury. Biomedicines, 12(5), 931. https://doi.org/10.3390/ biomedicines12050931.

[4] Zaitoun, T., Megahed, M., Elghoneimy, H., & et al. (2024). Renal arterial resistive index versus novel biomarkers for the early prediction of sepsis-associated acute kidney injury. Internal and Emergency Medicine, 19(4), 971-981. https:// doi. org/ 10.1007/s11739-023-03421-7.

[5] Leem, A. Y., Park, M. S., Park, B. H., & et al. (2017). Value of serum cystatin C measurement in the diagnosis of sepsis-induced kidney injury and prediction of renal function recovery. Yonsei Medical Journal, 58(3), 604-612. https://doi. org/ 10. 3349/ymj.2017.58.3.604.

[6] Onopiuk, A., Tokarzewicz, A., & Gorodkiewicz, E. (2015). Cystatin C: a kidney function biomarker. Advances in Clinical Chemistry, 68, 57-69. https://doi.org/10. 1016/bs.acc. 2014. 11. 003.

[7] Zhang, Z., Lu, B., Sheng, X., & et al. (2011). Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. American Journal of Kidney Diseases: the Official Journal of the National Kidney Foundation, 58(3), 356-365. https://doi.org/10.1053/j.ajkd.2011.03.019.

[8] Dharnidharka, V. R., Kwon, C., & Stevens, G. (2002). Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. American Journal of Kidney Diseases: the Official Journal of the National Kidney Foundation, 40(2), 221-226. https://doi.org/10. 1053/ ajkd. 2002. 34487.

[9] Wang, X., Tao, Y. H., Yang, J., & et al. (2020). Analysis of risk factors for acute kidney injury in patients with sepsis in the intensive care unit. Journal of Sichuan University (Medical Science Edition), 51(5), 708-713.

[10] Wei, M. B., Zhang, Z. Q., Ma, Z., & et al. (2021). Predictive value analysis of serum cystatin C combined with Acute Physiology and Chronic Health Evaluation II score for sepsis-associated acute kidney injury. Journal of Clinical Internal Medicine, 38(9), 619-622.

[11] Zhou, W. J., Zhang, N., Zhao, T., & et al. (2025). Predictive value of inflammatory indicators and serum cystatin C for prognosis in patients with sepsis-associated acute kidney injury. Chinese Critical Care Medicine, 37(3), 275-279.

[12] Chen, D. C., Potok, O. A., Rifkin, D., & et al. (2022). Advantages, limitations, and clinical considerations in using cystatin C to estimate GFR. Kidney360, 3(10), 1807-1814. https://doi.org/10.34067/kid.0000000000000971.

[13] Lima, C., Gorab, D. L., Fernandes, C. R., & et al. (2022). Role of proenkephalin in the diagnosis of severe and subclinical acute kidney injury during the perioperative period of liver transplantation. Practical Laboratory Medicine, 31, e00278. https://doi.org/10.1016/j.plabm.2022.e00278.

[14] Rosenqvist, M., Bronton, K., Hartmann, O., & et al. (2019). Proenkephalin a 119-159 (penKid) - a novel biomarker for acute kidney injury in sepsis: an observational study. BMC Emergency Medicine, 19(1), 75. https://doi.org/ 10.1186/ s12873-019-0257-8.

[15] Ji, B. K., Xie, Z. N., Pu, X. H., & et al. (2025). Proenkephalin a 119-159 as a biomarker for predicting sepsis-associated acute kidney injury. International Urology and Nephrology. https://doi.org/10.1007/s11255-025-04362-3.

[16] Dépret, F., Hollinger, A., Cariou, A., & et al. (2020). Incidence and outcome of subclinical acute kidney injury using penKid in critically ill patients. American Journal of Respiratory and Critical Care Medicine, 202(6), 822-829. https://doi.org/ 10. 1164/ rccm.201911-2175OC.

[17] Schaalan, M., & Mohamed, W. (2017). Predictive ability of circulating osteoprotegerin as a novel biomarker for early detection of acute kidney injury induced by sepsis. European Cytokine Network, 28(2), 52-62. https://doi.org/ 10.1684/ ecn. 2017. 0394.

[18] Niu, X., Wang, C., Li, H., & et al. (2024). Role of OPG/RANKL/RANK/TLR4 signaling pathway in

sepsis-associated acute kidney injury. BMC Nephrology, 25(1), 205. https://doi.org/10.1186/s12882-024-03872-8.

[19] Wang, F., Zhou, L., Eliaz, A., & et al. (2023). The potential roles of galectin-3 in AKI and CKD. Frontiers in Physiology, 14, 1090724. https://doi.org/10.3389/fphys.2023.1090724.

[20] Mueller, T., Leitner, I., Egger, M., & et al. (2015). Association of the biomarkers soluble ST2, galectin-3 and growth-differentiation factor-15 with heart failure and other non-cardiac diseases. Clinica Chimica Acta; International Journal of Clinical Chemistry, 445, 155-160. https://doi.org/ 10.1016/ j.cca.2015.03.018.

[21] Sun, H., Jiang, H., Eliaz, A., & et al. (2021). Galectin-3 in septic acute kidney injury: a translational study. Critical Care (London, England), 25(1), 109. https://doi.org/10. 1186/ s13 054-021-02536-3.

[22] H, Y., R, Y., J, W., & et al. (2024). Diagnostic value of serum ficolin-3 and gal-3 in sepsis complicated with acute kidney injury. International Journal of General Medicine, 17. https://doi.org/10.2147/IJGM.S448217.

[23] Liu, L., Chen, F., Liu, K., & et al. (2025). The KLF4/galectin-3 cascade is a key determinant of tubular cell death and acute kidney injury. International Journal of Biological Sciences, 21(13), 5802-5820. https://doi.org/10.7150/ijbs.104247.

[24] Formenti, P., Gotti, M., Palmieri, F., & et al. (2024). Presepsin in critical illness: current knowledge and future perspectives. Diagnostics (Basel, Switzerland), 14(12), 1311. https://doi.org/ 10. 3390/ diagnostics14121311.

[25] Ali, F. T., Ali, M. A. M., Elnakeeb, M. M., & et al. (2016). Presepsin is an early monitoring biomarker for predicting clinical outcome in patients with sepsis. Clinica Chimica Acta; International Journal of Clinical Chemistry, 460, 93-101. https://doi.org/10.1016/j.cca.2016.06.033.

[26] Shimoyama, Y., Umegaki, O., Kadono, N., & et al. (2021). Presepsin and prognostic nutritional index are predictors of septic acute kidney injury, renal replacement therapy initiation in sepsis patients, and prognosis in septic acute kidney injury patients: a pilot study. BMC Nephrology, 22(1), 219. https://doi.org/10.1186/s12882-021-02425-8.

[27] Shimoyama, Y., Umegaki, O., Kadono, N., & et al. (2022). Presepsin and platelet to lymphocyte ratio predict the progression of septic subclinical acute kidney injury to septic acute kidney injury: a pilot study. BMC Research Notes, 15(1), 212. https://doi.org/10.1186/s13104-022-06102-7.

[28] Han, S., Kim, M. J., Ko, H. J., & et al. (2023). Diagnostic and prognostic roles of C-reactive protein, procalcitonin, and presepsin in acute kidney injury patients initiating continuous renal replacement therapy. Diagnostics (Basel, Switzerland), 13(4), 777. https://doi.org/10.3390/diagnostics13040777.

[29] Guo, J., & Guo, F. M. (2023). Research progress on biomarkers and molecular mechanisms of sepsis-associated acute kidney injury. Chinese Journal of Emergency Medicine, 32(2), 269-274.

[30] Zhou, J., Ye, Y., Chen, Z., & et al. (2024). Upregulation of peripheral blood NLRP3 and IL-18 in patients with acute kidney injury in sepsis and its clinical significance. Immunity, Inflammation and Disease, 12(12), e70113. https://doi.org/10. 1002/ iid3. 70113.

[31] Wu, Y. L., Zhou, W. J., Li, X. L., & et al. (2022). Correlation between serum Nod-like receptor protein 3 and interleukin-18 levels and disease severity in patients with sepsis-associated acute kidney injury. Journal of Practical Medicine, 38(4), 484-488.

[32] Zhao, L., Guo, W. J., Wang, H. S., & et al. (2025). Expression and prognostic value of serum Nrf2, NLRP3 and IL-18 in elderly patients with sepsis complicated with acute kidney injury. International Journal of Geriatric Medicine, 46(4), 451-456.

[33] Xie, Y., Huang, P., Zhang, J., & et al. (2021). Biomarkers for the diagnosis of sepsis-associated acute kidney injury: systematic review and meta-analysis. Annals of Palliative Medicine, 10(4), 4159-4173. https://doi.org/ 10.21037/ apm-20-2718.

[34] Ichimura, T., Asseldonk, E. J. P. V., Humphreys, B. D., & et al. (2008). Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. Journal of Clinical Investigation, 118(5), 1657-1668. https:// doi. org/10.1172/JCI34587.

[35] Shao, X., Tian, L., Xu, W., & et al. (2014). Diagnostic value of urinary kidney injury molecule 1 for acute kidney injury: a meta-analysis. PLOS One, 9(1), e84131. https://doi.org/10. 1371/ journal. pone.0084131.

[36] Bonventre, J. V. (2009). Kidney injury molecule-1 (KIM-1): a urinary biomarker and much more. Nephrology, Dialysis, Transplantation, 24(11), 3265-3268. https://doi.org/10. 1093/ ndt/ gfp471.

[37] Brozat, J. F., Harbalioğlu, N., Hohlstein, P., & et al. (2024). Elevated serum KIM-1 in sepsis correlates with kidney dysfunction and the severity of multi-organ critical illness. International Journal of Molecular Sciences, 25(11), 5819. https://doi.org/10.3390/ijms25115819.

[38] Tu, Y., Wang, H., Sun, R., & et al. (2014). Urinary netrin-1 and KIM-1 as early biomarkers for septic acute kidney injury. Renal Failure, 36(10), 1559-1563. https://doi.org/10.3109/ 0886022X. 2014.956709.

[39] Liu, L. Z., Zeng, M. J., & Jiang, J. B. (2020). Role of NGAL, KIM-1 and PCT as biomarkers in sepsis-associated acute kidney injury. Genomics and Applied Biology, 39(3), 1408-1413.

[40] Jin, T. T., Lin, X., You, W. Y., & et al. (2025). Levels of THBS1, TRAF-6, KIM-1 and NLRP3 in patients with sepsis-associated acute kidney injury and their relationship with disease severity. Chinese Journal of Nosocomiology, 35(4), 518-522.

[41] Marakala, V. (2022). Neutrophil gelatinase-associated lipocalin (NGAL) in kidney injury - a systematic review. Clinica Chimica Acta; International Journal of Clinical Chemistry, 536, 135-141. https://doi.org/10. 1016/j.cca. 2022. 09. 013.

[42] Zappitelli, M., Washburn, K. K., Arikan, A. A., & et al. (2007). Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. Critical Care (London, England), 11(4), R84. https://doi.org/10.1186/cc6080.

[43] Han, Y., Ning, W., Lu, J., & et al. (2026). Combined predictive value of serum NGAL, CysC, urinary NAG, and eGFR for sepsis-associated acute kidney injury in patients in ICU. Saudi Medical Journal, 47(5), 877-883. https://doi.org/ 10.15537/smj. 2026.5. 20250841.

[44] Sepsis and AKI in clinical emergency room patients: the role of urinary NGAL. (n.d.). [EB/OL]. [2025-10-16].

[45] Ya-Fen, Z., Jing, C., Yue-Fei, Z., & et al. (2024). Reduction in NGAL at 48 h predicts the progression to CKD in patients with septic associated AKI: a single-center clinical study. International Urology and Nephrology, 56(2), 607-613. https://doi.org/10.1007/s11255-023-03804-2.

[46] Kim, H., Hur, M., Lee, S., & et al. (2017). Proenkephalin, neutrophil gelatinase-associated lipocalin, and estimated glomerular filtration rates in patients with sepsis. Annals of Laboratory Medicine, 37(5), 388-397. https://doi.org/10. 3343/ alm. 2017.37.5.388.

[47] Hu, Y. F., Jia, J., & Li, G. F. (2023). Research progress of C-C motif chemokine ligand 14. Journal of China Medical University, 52(10), 928-933.

[48] Hoste, E., Bihorac, A., Al-Khafaji, A., & et al. (2020). Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. Intensive Care Medicine, 46(5), 943-953. https://doi.org/10.1007/s00134-020-06016-4.

[49] Fu, Y. (2024). Early prediction study of persistent acute kidney injury in adult critically ill patients [Dissertation]. Hebei Medical University.

[50] Licheng, N., Jia, H., Jiang, Y., & et al. (2024). Predictive performance of two types of urinary biomarkers for renal non-recovery in sepsis-associated acute kidney injury: a prospective observational study. BMC Nephrology, 25(1), 153. https://doi.org/10.1186/s12882-024-03764-x.

[51] Jiang, W., Zhang, Y., Weng, J., & et al. (2025). Explainable machine learning model for predicting persistent sepsis-associated acute kidney injury: development and validation study. Journal of Medical Internet Research, 27, e62932. https://doi.org/10.2196/62932.

[52] Jiang, W., & Zheng, R. Q. (2022). Research progress on the clinical application value of tissue inhibitor of metalloproteinase-2 combined with insulin-like growth factor-binding protein 7 in sepsis-associated acute kidney injury. Chinese Critical Care Medicine, 34(1), 105-109.

[53] Honore, P. M., Nguyen, H. B., Gong, M., & et al. (2016). Urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 for risk stratification of acute kidney injury in patients with sepsis. Critical Care Medicine, 44(10), 1851-1860. https://doi.org/10.1097/ CCM. 00000 00000001822.

[54] Zhang, Q., Yang, B., Li, X., & et al. (2025). Biomarkers of cell cycle arrest, microcirculation dysfunction, and inflammation in the prediction of SA-AKI. Scientific Reports, 15(1), 8023. https://doi.org/10.1038/s41598-025-92218-1.

[55] Xie, Y., Ankawi, G., Yang, B., & et al. (2019). Tissue inhibitor metalloproteinase-2 (TIMP-2) • IGF-binding protein-7 (IGFBP7) levels are associated with adverse outcomes in patients in the intensive care unit with acute kidney injury. Kidney International, 95(6), 1486-1493. https://doi.org/10. 1016/j. kint.2018.12.024.

[56] Maizel, J., Daubin, D., Vong, L. V., & et al. (2019). Urinary TIMP2 and IGFBP7 identifies high risk patients of short-term progression from mild and moderate to severe acute kidney injury during septic shock: a prospective cohort study. Disease Markers, 2019, 3471215. https://doi.org/10. 1155/2019/ 347 12 15.

[57] Ning, S., Chen, J., Ma, J., & et al. (2026). Predicting renal replacement therapy requirement in sepsis-associated acute kidney injury using furosemide stress testing and urinary biomarkers. Journal of Visualized Experiments: JoVE, (233). https://doi.org/10.3791/66872.

[58] Gao, R. Y., Han, Y. Z., Li, W. X., & et al. (2022). Research progress on the relationship between calprotectin and sepsis. Chinese Journal of Critical Care Medicine, 42(1), 87-91.

[59] Huang, L., Li, J., Han, Y., & et al. (2016). Serum calprotectin expression as a diagnostic marker for sepsis in postoperative intensive care unit patients. Journal of Interferon & Cytokine Research: the Official Journal of the International Society for Interferon and Cytokine Research, 36(10), 607-616. https:// doi. org/ 10.1089/jir.2016.0027.

[60] Chen, J., Liu, Z., Zhou, F., & et al. (2025). Assessment of S100A8/A9 and resistin as predictive biomarkers for mortality in critically ill patients with sepsis. Frontiers in Cellular and Infection Microbiology, 15, 1555307. https://doi.org/10. 3389/ fcimb. 2025.1555307.

[61] Xu, J. R., Cao, S. Y. W., Ge, Z. H., & et al. (2018). Study on the early diagnostic value of blood and urinary calprotectin, IL-18 and serum creatinine for sepsis-associated acute kidney injury in mice. Medical Journal of Communications, 32(1), 14-17.

[62] Qian, J., Xu, J. R., Ge, Z. H., & et al. (2019). Early diagnostic value of blood and urinary calprotectin for sepsis-associated acute kidney injury. Chinese Journal of Clinical Rational Drug Use, 12(22), 133-134.

[63] Shi, W., Wan, T. T., Li, H. H., & et al. (2023). Blockage of S100A8/A9 ameliorates septic nephropathy in mice. Frontiers in Pharmacology, 14, 1172356. https://doi.org/10. 3389/fphar. 2023. 1172356.

[64] Zhang, J. N., Gong, R., Wang, Y. Q., & et al. (2025). Critical role of S100A9 in sepsis-associated acute kidney injury: mechanistic insights through pyroptosis pathway modulation. Inflammation, 48(4), 1879-1899. https://doi.org/ 10.1007/ s10 753-025-02127-4.